Patent Application of

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for

ENTERIC DELIVERY OF (–)-HYDROXYCITRIC ACID

BACKGROUND OF THE INVENTION

1. Field Of The Invention

The invention is directed toward novel compositions in which (–)-hydroxycitric acid and the salts of (–)-hydroxycitric acid, including its esters and amides, are rendered nonreactive to acids and prevented from release prior to entry into the appropriate region of the digestive tract by means of delivery via enteric and enteric coated capsules, soft gelatin capsules (softgels) and tablets.

2. Description Of Prior Art

(–)-Hydroxycitric acid (abbreviated herein as HCA) a naturally-occurring substance found chiefly in fruits of the species of *Garcinia*, and several synthetic derivatives of citric acid have been investigated extensively with regard to their ability to inhibit the production of fatty acids from carbohydrates, to suppress appetite, and to inhibit weight gain. (Sullivan, A.C., et al., American Journal of Clinical Nutrition 1977;30:767.) Numerous other benefits have been attributed to the use of HCA, including, but not limited to an increase in the metabolism of fat stores for energy and an increase in thermogenesis (the metabolism of energy sources to produce body heat in an otherwise wasteful cycle). The commonly offered explanation for the effects of HCA is that this compound inhibits the actions of cytoplasmic (cytosolic) ATP:citrate lyase. (D. Clouatre and M. E. Rosenbaum, *The Diet and Health Benefits of HCA (Hydroxicitric Acid)*, 1994.)

Weight loss benefits were attributed to HCA, its salts and its lactone in United States Patent 3,764,692 granted to John M. Lowenstein in 1973. Lowenstein described a variety of possible pharmaceutical salts of HCA based upon alkali metals, e.g., potassium and sodium, and alkaline earth metals, e.g., calcium and magnesium. The production of the potassium salt of HCA had been characterized in the scientific literature previous to Lowenstein's patent, but not in regard to

its weight-loss properties. Research into HCA by scientists at the pharmaceutical firm of Hoffmann-La Roche revealed that the lactone form of HCA is far less effective than is the sodium salt of HCA for weight loss purposes, in part because the lactone form lacks the proper affinity for the receptor then known to be a target of the actions of HCA. However, the sodium salt has disadvantages for long-term administration, both because sodium possesses no positive metabolic effects with regard to obesity and because sodium has potential hypertensive actions as well as other drawbacks. Potassium, as a ligand for HCA, does not possess the disadvantages associated with sodium. Moreover, the absorption of the potassium salt of HCA is considered to be superior to that of the sodium salt owing to the greater rate of uptake of potassium in relation to sodium in most tissues.

Free (–)-hydroxycitric acid, calcium, magnesium and potassium salts of HCA and poorly characterized mixtures of two or more of these minerals, usually substantially contaminated with sodium, currently exist on the American market. Calcium/sodium salts have been sold widely since at least as early as 1992. Most of the HCA sold to date consists of calcium salts of varying degrees of purity and, more recently, of poorly characterized calcium and potassium mixtures. Aside from the relatively pure potassium salt, all of these HCA forms suffer from problems in assimilation, a fact attested to by poor performance in controlled weight loss trials.

For instance, the free acid form of (–)-hydroxycitric acid is extremely ionic and does not pass readily through the gut membrane. Free HCA has several further disadvantages. It undergoes rapid lacontonization, and, again, the lactone form has no appreciable physiological activity. Indeed, inclusion of any of the currently available mineral salts of HCA in a prepared beverage of acidic pH will lead to the development of the HCA lactone over time. The free acid form, moreover, has a tendency to be bound up and made unavailable to the body by soluble and insoluble fibers as well as by many other compounds. Likewise the potassium and sodium salts, if placed even only briefly in acidic or flavored beverages, typically will undergo color change or exhibit other signs of having undergone chemical interaction with the contents of the beverage. Finally, although there is some evidence to the effect that the free acid (not the lactone) is more active than is the calcium salt of HCA, there is also good evidence that the free acid and the lactone both are irritating to the GI-tract if consumed regularly in large amounts. Thus although patents exist for the use of free (–)-hydroxycitric acid concentrate in food products (for

instance, United States Patent 5,536,516), the art taught therein offers no particular advantages for weight loss nor for other medicinal purposes.

The calcium and magnesium salts of HCA are poorly absorbed from the gastrointestinal tract because they are poorly soluble in aqueous media and because both of these minerals are saponified by bile acids and fats in the gut and/or are bound up by soluble and insoluble fibers or other substances in the diet or secreted during digestion. Some of these problems have been pointed out by medical researchers and admitted in print by at least one primary manufacturer of HCA products. (Heymsfield, Steven B, et al. JAMA 1998;280(18):1596-1600; Letters, JAMA 1999;282:235.) Moreover, there is no evidence that merely making calcium and magnesium salts of HCA more soluble, such as can be accomplished by adding small amounts of potassium and/or sodium and/or lactone, will solve the problem of assimilation. HCA is known to have three separate binding points, and simple chemical experimentation quickly shows that divalent ions, such as those of calcium and magnesium, cannot be readily separated by the application of other acids, such as human gastric acid, from the HCA once these minerals have been reacted with it. The action of stomach acid, however, may free one of the two valences of calcium or magnesium for attachment to fats, bile acids, gums, fibers, pectins, and so forth and so on, which is an undesirable outcome. Aside from such factors, it is also the case that calcium uptake from the gut is highly regulated and under normal circumstances does not exceed approximately 35 percent of that found in foods and supplements, with the uptake declining as the dosage increases. This is a known and accepted aspect of nutrition and physiology which argues against the use of calcium as a major ligand for any compound that needs to be taken in relatively large dosages, such as HCA.

One leading producer of HCA products at the date of this filing still has posted at its own internet website (http://www.interhealthusa.com/research/citrimax) data indicating the poor bioavailability of its calcium/potassium salt of HCA, to wit: "Researchers at the University of California, Berkeley, found that absorption of (–)hydroxycitric acid (Super CitriMax®) peaked 2 hours after administration, and that the compound remained in the blood for more than 9 hours after ingestion. Eating a meal shortly after taking Super CitriMax® reduced its absorption by about 60%. Source: Loe Y, Bergeron N, Phan J, Wen M, Lee J, Schwarz J-M, Time Course of Hydroxycitrate Clearance in Fasting and Fed Humans, FASEB Journal, 15 4:632, Abs. 501.1,

2001." Rather more significantly, the same researches using the same product demonstrated via blood tests that uptake of this product on an empty stomach typically is on the order of only approximately 20 percent. (Loe YC, Bergeron N, et al. Gas chromatography/mass spectrometry method to quantify blood hydroxycitrate concentration. Anal Biochem. 2001 May 1;292(1):148-54.) Hence, except under ideal circumstances, normal uptake of even a supposedly premium product is probably not much more than 10 percent of that ingested.

For weight loss and other purposes, a minimally effective amount of HCA derived from its calcium salt requires the administration of between 12 and 15 grams of a 50% material, and this amount of calcium (–)-hydroxycitrate may lead to undesirably elevated levels of binding and excretion of other dietary minerals, such as zinc, aside from presenting difficulties in administration. Animal trials (see United States Patent No. 6,476,071) have further demonstrated that in order for the potassium salt to be maximally effective, the ligand must be fully bound to the HCA with only trivial amounts of contaminants, including other minerals or fibers or sugars. Hence the calcium and magnesium salts, certain specialty preparations aside, either alone or in the form of various mixtures together or in combination with the potassium and sodium salts, are not preferred delivery forms for HCA.

Several recent international patent applications and at least one U.S. Patent claim to have greatly improved the efficacy of HCA via its delivery as calcium, magnesium and admixtures of salts. For instance, WO 99/03464, filed 28 January 1999, claims special benefits for "hydroxycitric acid compositions which comprise approximately 14 to 26% by weight of calcium, and approximately 24 to 40% by weight of potassium or approximately 14 to 24% by weight of sodium, or a mixture thereof, each calculated as a percentage of the total hydroxycitric acid content of the composition, together with dietary supplements and food products containing such compositions and methods for utilizing such compositions, dietary supplements and food products to reduce body weight in mammals are disclosed." However as already noted above, research performed specifically with this compound showed that its assimilation is exceedingly poor even when taken on an empty stomach (Loe YC, et al. Gas chromatography/mass spectrometry method to quantify blood hydroxycitrate concentration. Anal Biochem. 2001 May 1;292(1):148-54) and that eating a meal shortly after taking it reduced its absorption by about 60%. (Loe Y, et al. Time Course of Hydroxycitrate Clearance in Fasting and Fed Humans,

FASEB Journal, 15,4:632, Abs. 501.1, 2001.)

No proof is offered in WO 99/03464 that the proposed compound is superior to fully reacted calcium HCA with regard to assimilation. It also should be noted that inasmuch as *Garcina cambogia* is typically salted for drying in Asia with the subsequent extracts including large amounts of sodium and inasmuch as calcium salts of HCA have been sold in the US since at least 1992, the realization that mixing a divalent ligand with a monovalent ligand in reacting HCA will yield a soluble, yet increasingly nonhygroscopic salt was known at least as far back as 1992. Several of the early Indian-supplied "potassium" salts were, in fact, mixtures of calcium, potassium and sodium (–)-hydroxycitrate. Of course, the amount of sodium allowed with this product will be in excess of that allowed on low sodium diets and additional sodium is ill-advised on any modern diet. The present inventors, in point of fact, used a CaKHCA salt identical to that described by WO 99/03464 in animal trials along with other arms utilizing a poorly reacted potassium salt and a fully reacted potassium salt. The product described in WO 99/03464 was much inferior to either potassium salt in middle-aged rats fed a 30 percent fat diet. These results can be found in United States Patent No. 6,476,071 B1.

Another application by Majeed, et al., WO 00/15051, seeks to make calcium (–)-hydroxycitrate soluble by under-reacting the material, i.e., leaving a substantial amount of HCA lactone in the finished product. This procedure, however, does little to improve the uptake of HCA. The problems with the lactone are discussed above, and the lactone in large amounts is known to be irritating. (Ishihara K, Oyaizu S, Onuki K, Lim K, Fushiki T. Chronic (-)-hydroxycitrate administration spares carbohydrate utilization and promotes lipid oxidation during exercise in mice. J Nutr. 2000 Dec;130(12):2990-5.) Making calcium soluble, again, does nothing to prevent its saponification in the gut nor does this improve the general rate of assimilation of calcium. One must assume that the rate of uptake by the compound taught in this invention will be even worse than that tested by Loe Y, et al., as indicated with WO 99/03464 above. In any event, the process proposed in WO 00/15051 was anticipated by others and had already been published in English in 1997 (Sawada, H., et al. Effects of liquid garcinia extract and soluble garcinia powder on body weight change. Journal of Japan Oil and Chemicals/Nihon Yukagaku Kaishi 1997 December;46, 12:1467-1474) and many months earlier in Japanese.

A much more promising application is WO 02/014477, first applied for in 17 August 2000,

which relates to a composition comprising hydroxycitric acid (HCA) in combination with either one or both of garcinol and anthocyanin. However, one should note that the effects reported are not overwhelming. In eight weeks, the average weight loss, for instance, was 4 pounds versus 2.5 pounds for control. Using a higher dosage of potassium (–)-hydroxycitirate alone, Clouatre et al. in United States Patent 6,447,807 reported an average weight loss over a three week period of 3 pounds per week. Still to be determined is whether the additive effect shown in WO 02/014477 extends beyond the mild response reported if higher dosages of either component are ingested. Moreover, in practice garcinol is a common contaminant of HCA products, hence this application is claiming a special virtue for a compound already typically present in the salts which have been used for clinical studies, i.e., extracts rather than synthesized pure (–)-hydroxycitric acid salts.

Finally, US Patent 6,221,901 discusses the preparation and employments of magnesium (–)-hydroxycitirate. Leaving aside the many difficulties with the claims of this patent, the dosages used to achieve the indicated results were massive. To achieve a hypotensive effect, for instance, Shrivastava et al. fed their animals 500 mg/kg magnesium (–)-hydroxycitirate. Using the standard 5:1 multiplier for rat to human data, the dose of magnesium hydroxycitrate employed by Shrivastava et al. is equivalent to a human ingesting 100 mg/kg/day or 7 grams for the average-sized human subject. Of this amount, 45% would be elemental magnesium, hence we have the equivalent of a human ingesting approximately 3.15 grams of magnesium. The *Recommended Dietary Allowances*, 10th edition (National Research Council, 1989), indicates that most humans begin to suffer diarrhea at more than 350 mg/day. In other words, the test dose used by Shrivastava et al. is nearly 10 times the dose at which side effects would normally be expected to begin to appear. The diarrhea induced itself would lower blood pressure rapidly. Hence, with normal magnesium (–)-hydroxycitirate not only is there poor uptake, but also there is the danger of osmotic diarrhea. Clearly this compound is not the answer to issues of improving the delivery of (–)-hydroxycitirate.

The preferred salt of HCA for pharmaceutical use is potassium (–)-hydroxycitrate (abbreviated herein as KHCA). The mineral potassium is fully soluble, as is its HCA salt, and is known to possess cell membrane permeability which is 100 times greater than that possessed by sodium. However, the potassium salt of HCA, as is also true of the sodium salt, is extremely hygroscopic and thus not suitable under normal circumstances for the production of dry delivery

forms. In drawing moisture to itself, KHCA will also tend to bind to available binding sites of compounds in its immediate environment, and this action often later will markedly impede the assimilation of KHCA from the gut. KHCA is also not suitable for liquid delivery forms inasmuch as KHCA in solution will slowly lactonize to an equilibrium which is dependent upon the pH. One recent patent (United States Patent 5,783,603) does teach a technique for the production of KHCA, but this material is nonhygroscopic only under the conditions mentioned specifically in that patent, to wit, "milling, sifting, blending and packing said dried precipitate under nitrogen to obtain said potassium hydroxycitric acid [*sic*] composition." If left in the open air outside of a humidity-controlled environment, the KHCA produced according to that patented method will begin to absorb moisture within a few minutes. Except as a very minor ingredient, it cannot be used as a component of dry pharmaceutical or nutriceutical preparations. The nature of the claims of this United States Patent 5,783,603 are also unclear inasmuch as in United States Patent 3,764,692 granted to John M. Lowenstein in 1973 described a variety of possible pharmaceutical salts of HCA based upon alkali metals, which in the body of the patent are explicitly defined as including potassium and sodium. Moreover, Majeed, et al., of United States Patent 5,783,603, in their own application WO 02/014477 describe United States Patent 5,783,603 as a production or process patent.

Only three pieces of prior art (the present inventors' own United States Patent 6,447,807 and Applications No. 10/303,117 and No. 10/447,992) teach methods for making the hygroscopic salts of (–)-hydroxycitric acid workable and for controlling the delivery of HCA salts in general. Both propose methods distinct from that contained herein. The paucity of methods for producing a controlled release form of HCA, regardless of the salt used, has led to a problem in the delivery of the drug. Tests performed to establish the appetite-suppressing effects of HCA found that a single large oral dose or two divided oral doses totaling one fourth the size of the single dose resulted in a 10% or greater reduction in food consumption in experimental animals fed a high-sugar diet. This result continued over many weeks with the chronic ingestion of HCA. The requirement for at least two divided doses of HCA for efficacy is the only thoroughly established procedure to date. However, as indicated above, relatively large doses of HCA are required to achieve suitable effects. On an empty stomach using typical delivery methods, only 20% absorption takes place. The presentation of food within 30 to 60

minutes of consumption cuts this rate in half.

The present invention indicates a simple novel composition by which the salts, esters and amides of (–)-hydroxycitric acid can be delivered into the small intestine without being exposed to contact with the low pH contents of the stomach, hence without being exposed to conditions that encourage lactonization and the unwanted binding to digestive contents. Despite a decade of research into HCA at a major pharmaceutical company and another decade of free sale of HCA products in the general marketplace, the present invention is the first to teach its novel approach to the delivery of HCA such as to avoid degradation and other undesirable changes in the upper digestive tract.

SUMMARY OF THE INVENTION

The present invention resolves problems with regard to the use of the potassium, sodium and other salts, esters and amides of (–)-hydroxycitric acid. A principle is provided by which these items, when ingested orally, are delivered protected against acid degradation, lactonization and undesirable ligand binding such as take place when HCA is exposed to acidic environments or other challenging conditions. In particular, the salts, esters and amides of HCA according to the invention are delivered via enteric vehicles, such as enteric and enteric coated capsules, soft gelatin capsules (softgels) and tablets. Coatings may be applied externally or, in the case of capsules and soft gelatin capsules, may be incorporated into the gelatin shell. The invention describes these novel enteric compositions.

Objects and Advantages

The potassium salt of (–)-hydroxycitric acid is the most efficacious form of HCA to be used for human weight loss and for other pharmaceutical and/or neutraceutical purposes, followed secondarily for these purposes by the sodium salt. These and other forms of HCA, when dissolved in liquid, are reactive with a large number of compounds (tannins, gums, fibers, pectins, and so forth), dissolve in and are reactive in stomach acid, and otherwise readily suffer losses in pharmacological availability.

The object of the current invention is to prevent such degradation and loss. Previously, the

inventors have demonstrated that coatings may be applied directly to powders comprised of HCA salts. However, it is possible to avoid such coatings and yet still render these salts impervious to degradation in the stomach with the obvious attendant advantages. The present invention teaches that this may be accomplished by applying special coatings externally to dosage forms of HCA, such as capsules, soft gelatin capsules and tablets.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The raw material is the potassium salt of (–)-hydroxycitric acid which has been produced as an extract of *Garcinia cambogia*, other *Garcinia* species or by synthesis. In hydrated form it is a viscous deep brown. It has a earthy smell and contains approximately 6 parts by weight of solids per liter of fluid. The novel concept of this application is to show that a proper coating can be applied to dosage forms containing potassium HCA or other salts and mixtures of salts of HCA and HCA derivatives, such as amides and esters, to yield a dosage delivery vehicle with a more favorable delivery profile.

Methods Of Preparation

By the teachings herein disclosed, (–)-hydroxycitric acid salts and derivatives can be prepared as capsules, soft gelatin capsules (softgels) and tablets. These forms subsequently can be coated with shellac, cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinyl acetate phthalate, cellulose acetate trimaleate, Resomer® RG enteric polymer, Eudragit L55® and other methacrylic acid and methacrylic acid esters, zein and other known enteric products or mixtures thereof, depending upon the properties desired in the finished product. These enteric coating materials may be applied with or without plasticizers, such as acetylated glycerides, diethylphthalate, etc., and by means known in the art. Another method is to melt a gelatin mixture with the enteric material in the gelatin solution and make capsules after allowing the melt to fit around forms, which capsules are then filled with HCA and other materials. The HCA powders and granulates may be processed in various manners prior to being placed in the capsules, soft gelatin capsules (softgels) and tablets, for instance, placement in beadlets or microspheres, enteric coated microspheres, etc. In the case of the soft gelatin capsules, the HCA may be placed first in an oil or other suitable carrier. The percentage of coating applied is usually

between about 1-10%, with the most desirable amount normally being about 2 to 8% of the capsule or tablet weight. Work in a low humidity environment is desirable with the potassium and sodium salts.

The present invention employs, unless otherwise indicated, conventional techniques of pharmaceutical formulation, medicinal chemistry, biological testing and the like which are within the reach of one possessing ordinary skill in the art. Such techniques are explained fully in the literature.

EXAMPLE 1

Soft gelatin encapsulation is used for oral administration of drugs in liquid form. For this purpose, HCA may be provided in a liquid form by suspending it in oils, polyethylene glycol-400, other polyethylene glycols, poloxamers, glycol esters, and acetylated monoglycerides of various molecular weights adjusted such as to insure homogeneity of the capsule contents throughout the batch and to insure good flow characteristics of the liquid during encapsulation. The soft gelatin shell used to encapsulate the HCA suspension is formulated to impart enteric characteristics to the capsule to ensure that the capsule does not disintegrate until it has reached the small intestine. The basic ingredients of the shell are gelatin, one or more of the enteric materials listed above, plasticizer, and water. Care must be exercised in the case of softgels to use the less hygroscopic salts and forms of HCA or to pretreat the more hygroscopic salts to reduce this characteristic. The carrier may need to be adjusted depending on the HCA salt, ester or amide used so as to avoid binding of the ingredients to the carrier. Water should never be used as a carrier. Various amounts of one or more plasticizer are added to obtain the desired degree of plasticity and to prevent the shell from becoming too brittle.

EXAMPLE 2

Many enteric coatings are used routinely in the pharmaceutical industry. Coatings delivered via organic solvents are to be preferred when working with the hygroscopic salts of HCA, such as potassium or sodium (–)-hydroxycitrate, although water-based deliveries are acceptable which

non-hygroscopic salts, such as calcium (–)-hydroxycitrate. Ammoniated water may likewise acceptable as a substitute for organic solvents when non-hygroscopic HCA salts are being employed. Following are several standard coating formulations that can be used successfully with all forms of HCA and with hard shell capsules, soft gelatin capsules and properly prepared tablets. For instance, a hard shell capsule might be filled with 500 mg potassium-calcium (–)-hydroxycitrate and then coated according to standard procedures using one of these formulations. For hard shell and soft gelatin capsules, the HCA salt, carrier (if needed) and optional additional ingredients are first mixed to prepare the interior formulation. The formulation is then encapsulated and the capsule is coated with a dispersion of enteric coating components. With tablets, the material is compressed according to normal procedures. The percentage of coating applied is usually between about 1-10%, with the most desirable amount normally being about 2 to 8% of the capsule or tablet weight.

Formulation	**% w/w**
1)	
Cellulose acetate phthalate (CAP)	8.5
Diethyl phthalate	1.5
Acetone	45.0
Denatured alcohol	45.0
2)	
Polyvinyl acetate phthalate	5.0
Acetylated glycerides	0.8
Methylene chloride	47.1
Denatured alcohol	47.1
3)	
Eudragit methacrylic acid and methacrylic acid esters	8.0
Acetone	46.0
Anhydrous alcohol	46.0
Plasticizer	as needed
4)	
Hydroxypropyl methylcellulose phthalate	5.0
Triacetin	0.5
Methylene chloride	47.25
Denatured alcohol	47.25

CONCLUSIONS

(–)-Hydroxycitrate has a multitude of metabolic functions. The literature teaches that the compound induces weight loss and decreases appetite in both animals and humans. When manipulated by normal methods, it is poorly delivered to the gastrointestinal tract because of its sensitivity to acids, digestive compounds and dietary ingredients. Without special precautions, (–)-hydroxycitric acid in its free acid form and in its salt forms will bind to numerous other compounds and thereby to become markedly less assimilable.

The present invention resolves problems with regard to the use of the potassium, sodium and other salts, esters and amides of (–)-hydroxycitric acid. A principle is provided by which these items, when ingested orally, are delivered protected against acid degradation, lactonization and undesirable ligand binding such as take place when (–)-hydroxycitric acid, its salts and derivatives are exposed to acidic environments or other challenging conditions. In particular, (–)-hydroxycitric acid and the salts, esters and amides of (–)-hydroxycitric acid according to the invention are delivered via enteric vehicles, such as enteric coated tablets, and also enteric and enteric coated capsules and soft gelatin capsules (softgels). Coatings may be applied externally or, in the case of capsules and soft gelatin capsules, may be incorporated into the gelatin shell. The invention describes these enteric compositions.